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08/967,243	11/05/97	LASKY	ATTY. DOCKET NO. MU
HM12/0121			L P0833P1C1
MERCHANT & GOULD ATTN. DIANE L. MARSCHANG 3100 NORWEST CENTER 90 SOUTH SEVENTH STREET MINNEAPOLIS MN 55402-4131			EXAMINER
			DATE MAILED: 01/21/00

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

#### OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 11/1/99
- ☐ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

- ☒ Claim(s) 1, 15, 25, 28 is/are pending in the application.
- Of the above, claim(s) 15-25 is/are withdrawn from consideration.
- ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- ☒ Claim(s) 1, 28 is/are rejected.
- ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- ☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- ☒ Notice of Reference Cited, PTO-892 ☒ NOTICE TO COMPLY WITH SEQUENCE RULES
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

### DETAILED ACTION

1. The request filed 11/1/99 (Paper No. 30) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/967,243 is acceptable and a CPA has been established. An Office Action on the CPA follows.

2. A restriction was required under 35 USC § 121 in the parent application, Paper No. 4 between the following Groups, as they read on pending claims.

- I. Claims 1 and 28, drawn to methods of inhibiting L-selectin binding with CD34.
- II. Claims 15-17, drawn to method of targeting active compounds with CD34-specific antibodies.
- III. Claim 19, drawn to methods of presenting carbohydrate antagonists of L-selectin-CD34 interactions.
- IV. Claim 20-25, drawn to bispecific molecules.

Applicant elected Group I with traverse in Paper No. 6.

This restriction requirement is hereby reiterated.

Accordingly, claims 15-25 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to the nonelected inventions.

Claims 2-14 and 26-27 have been canceled previously.

Claims 1 and 28 are under consideration and being acted upon.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. The rejections of record can be found in previous Office Actions (Paper Nos. 7/13/16/23/26).

Given the absence of additional rebuttal to the outstanding rejections of record in applicant's amendment, filed 11/1/99 (Paper No. 30); the rejections are maintained for the reasons of record.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825 (see the specification at page 10, line 22). However, this application fails to comply with the requirements set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence.

The following procedure is to be used for cases that contain the same sequence disclosure as the parent. The applicant need not submit a new computer readable form of the Sequence Listing in this rule 60 continuation. However, (1) the specification must contain a paper copy of the Sequence Listing, (2) applicant must request in writing that the CRF in the parent case be used to prepare a file for the offspring and (3) applicant must submit a statement that the paper copy of the Sequence Listing in the offspring is identical to the computer readable form submitted in the parent case.

Applicant is required to fulfill these requirements

5. Again, applicant should update the status of the parent applications on the first line of the specification. USSN 08/256, 418 is now abandoned. Also, applicant is invited to clarify whether PCT/US9403791 is a continuation or a continuation-in-part of USSN 08/056,054. Compare the first line of the specification and the Oath/Declaration.

6. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 7.

As pointed out previously, it was noted that applicant has amended the Brief Description of the Drawings to include Figure 2 and that there was no Figure 2.

Upon a review, it appears that figures as filed were misnumbered and that the labeling a figure as Figure 2 was missing when the application was filed. This appears to have led to applicant's amendment of the Brief Description of the Drawings. It is presumed that applicant will make the appropriate corrections to the figures themselves, when formal figures will be submitted. Applicant is invited to clarify this issue.

Applicant will submit formal drawings upon the indication of allowable subject matter.

7. Claims 1 and 28 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "inhibiting the binding of native L-selectin to peripheral lymphoid tissue" and "contacting said L-selectin".

Applicant's amendment, filed 10/5/97 (Paper No. 20), directs support to pages 1 and 3 of the specification.

The claims now recite inhibiting the binding of "L-selectin" rather than "L-selectin expressing cells" or "L-selectin interactions". Therefore, the claims read on inhibiting soluble L-selectin to peripheral lymphoid tissue rather than inhibiting L-selectin expressing cells from interacting with peripheral lymphoid tissue, as disclosed in the application as filed. Further, the recitation of "native L-selectin" is not readily apparent from the specification as filed. The specification as filed does not provide a written description or set forth the metes and bounds of these phrases. The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope and nature of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.

8. Claims 1 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as adhesion-based molecules can be species- and model-dependent, it is not clear that reliance on the identification of CD34 as L-selectin ligand and the expression of CD34 in various tissues and in certain inflammatory tissues accurately reflects the relative efficacy of the claimed methods for inhibiting the binding of L-selectin to peripheral lymphoid tissues in effective amounts sufficient to prevent or suppress the physiological conditions or symptoms which block the adhesive interactions between leukocytes (including lymphocytes, neutrophils and monocytes) and endothelial cells to treat pathological responses associated with leukocyte homing, including those encompassed by the number of inflammatory conditions disclosed in the specification as filed (see Therapeutic Applications on pages 17-20 of the specification).

As acknowledged in the Discussion on pages 31-33 of the instant specification; CD34 is glycosylated differently under different conditions and in different tissues. Further, this Discussion discloses that future investigations would determine whether various adhesion systems are utilized during acute and chronic inflammation. Therefore, the specification as filed lacks working examples.

Although CD34 isolated from murine lymph nodes binds L-selectin in vitro, CD34 is constitutively expressed on most endothelial cells and hemopoietic stem cells. There is insufficient guidance and direction as to how to use CD34 to inhibit L-selectin binding for the number of acute or chronic inflammatory conditions encompassed by the claimed methods.

With respect to "inhibiting the binding of native L-selectin to peripheral lymphoid tissue"; the following is noted. There is insufficient direction or guidance provided to assist one skilled in the art in therapeutic methods of "inhibiting the binding of native L-selectin to peripheral lymphoid tissue" in the appropriate physiological conditions or symptoms, wherein the L-selectin or soluble L-selectin is a target of such therapy. Again, the disclosed and intended therapeutic methods are drawn to inhibiting L-selectin mediated interactions and to inhibiting L-selectin expressing cells in patients of need. There is insufficient guidance and direction in the application as filed to treat patients in need, wherein the therapeutic modality is to inhibit L-selectin itself from binding to peripheral lymphoid tissue. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. It appears that undue experimentation would be required of one skilled in the art to practice the claimed methods using the teaching of the specification alone.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, *Biotechnology* 10: 383-389, 1992; see entire document, particularly page 386, column 3, paragraph 4) (892).

Ward et al. addresses the issues associated with selection of interventions of adhesion molecules as an approach to anti-inflammatory therapy (*Therapeutic Immunol.* 1: 165-171, 1994) (892). At the current time of the article (1994), in humans there are relatively few conditions in which there is clear-cut evidence of the presence and participation of given adhesion molecules in humans (page 166, column 1, paragraph 1).

Albelda et al. (*FASEB Journal* 8: 504-512, 1994) (1449) disclose that it is also disclosed that one of the most important lessons that has emerged from animal studies of CAMs is that there are distinct differences in the adhesion requirements for particular types of inflammation (pages 508-509, column 2, overlapping paragraph).

Although the animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. For example, most models including those associated with adhesion-/selectin-specific antagonists rely upon experimental protocols wherein the antagonist and the stimulus/insult occur at the same or nearly the same time. Blocking adhesion or immune responses is much easier to achieve under such controlled conditions than that experienced in the number of acute and chronic inflammatory conditions encompassed by the claimed invention.

For example, Welply et al. (*Biochimica et Biophysica Acta* 1197: 215-226, 1994) similarly disclosed the limitations of the use of L-selectin-specific antagonists for chronic diseases (see entire document, particularly section 5.3. Disease Targets).

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting the binding of L-selectin to peripheral lymphoid tissues in effective amounts sufficient to prevent or suppress the physiological conditions or symptoms which block the adhesive interactions between leukocytes (including lymphocytes, neutrophils and monocytes) and endothelial cells to treat pathological responses associated with leukocyte homing, including those encompassed by the number of inflammatory conditions disclosed in the specification as filed (see *Therapeutic Applications* on pages 17-20 of the specification).

9. Claim 28 stands objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The recitation of "CD34 isolated from peripheral lymph nodes" recited in claim 28 is essentially the same as that recited in claim 1 and does not further limit claim 1.

10. Claims 1 and 28 stand rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Butcher et al. (U.S. Patent No. 5,538,724; see entire document) essentially for the reasons of record set forth in the previous Office Actions (Paper No. 7/13/16/23/26).

Applicant's arguments and the examiner's rebuttal are of record.

Applicant's arguments have been fully considered but have not been found convincing for the reasons of record.

11. Claims 1 and 28 stand rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Lasky et al. (U.S. Patent No. 5,304,640) essentially for the reasons of record set forth in the previous Office Actions (Paper Nos. 7/13/16/23/26).

Applicant's arguments and the examiner's rebuttal are of record.

Applicant's arguments have been fully considered but have not been found convincing for the reasons of record.

Applicant's arguments relying upon the Lasky/Rosen/Singer declaration under 37 C.F.R. § 1.132 alone are not found persuasive.

12. Claims 1 and 28 stand rejected under 35 U.S.C. § 103 as being unpatentable over Butcher et al. (U.S. Patent No. 5,538,724) or Lasky et al. (U.S. Patent No. 5,304,640) in view of Lasky et al. (CSHSQB, 1992; 1449, #35), Berg et al. (J. Cell Biol., 1991; 1449, 1449, #8) or Imai et al. (J. Cell Biol. 1991; 1449, #28), Sutherland et al. (Leukemia, 1988; 1449, #51), Lasky et al. (U.S. Patent No. 5,098,833; 1449, #2), Watson et al. (Nature, 1991; 1449, #55), Fina et al. (Blood, 1990; 1449, #22) and Schlingemann et al. (Lab. Invest., 1990; 1449, #42) essentially for the reasons of record set forth in the previous Office Actions (Paper Nos. 7/13/16/23/26).

Applicant's arguments and the examiner's rebuttal are of record.

Applicant's arguments have been fully considered but have not been found convincing for the reasons of record.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.  
Patent Examiner  
Technology Center 1600  
January 18, 2000

*Phillip Gambel*

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING  
NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

08/967443

- ☐ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).
- ☐ 7.

Other: \_\_\_\_\_

**Applicant must provide:**

- ☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"
- ☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification
- ☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123  
For CRF submission help, call (703) 308-4212  
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.